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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/673,935	09/30/2003	William Michael Russell	035051/309049	2630

826 7590 07/25/2006

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 07/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/673,935	RUSSELL ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,19 and 21-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,21,22,24 and 25* is/are rejected.

7)☒ Claim(s) *19 and 23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 9/30/03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 18-19 and 21-25 are pending in the application.

[2] Applicant's preliminary amendment to the claims, filed on 5/9/2006, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's preliminary amendment to the specification, filed on 5/9/2006, is acknowledged.

Election/Restriction

[4] Applicant's election without traverse of Group I, original claims 18-19, in the reply filed on 5/9/2006 is acknowledged. Newly added claims 21-25 are drawn to the elected invention. Thus, claims 18-19 and 21-25 are being examined on the merits.

Priority

[5] Applicant's claim to domestic priority under 35 USC § 121 to US Application No. 09/862,660, filed on 5/21/2001, now US Patent 6,664,097, is acknowledged. Applicant's claim to domestic priority under 35 USC § 119(e) to US provisional application No. 60/206,372, filed on 5/23/2000, is acknowledged.

Information Disclosure Statement

[6] All references cited in the IDS filed on 9/30/2003 have been considered by the examiner. A copy of Form PTO-1449 is attached to the instant Office action.

Sequence Compliance

[7] As noted in the prior Office communication, there is no amendment directing entry of the substitute sequence listing filed on 12/15/2003 into the specification. In order to perfect the requirements for sequence compliance, applicant should include such an amendment in response to this Office action.

Specification/Informalities

[8] The attempt to incorporate subject matter into this application by reference to a hyperlink embedded in the specification (for example, page 12, line 9) is improper. Incorporation of subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP 608.01 regarding hyperlinks in the specification and 608.01(p), paragraph I regarding incorporation by reference.

Claim Objections

[9] Claim 24 is objected to as being grammatically incorrect in the recitation of "a polynucleotide that differ from" and it is suggested that "differ" be replaced with "differs."

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[10] Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 18, part (a) is indefinite in the recitation of "hybridizes...under stringent conditions represented by..." because it is unclear as to whether the hybridization conditions are intended as being limited to those set forth in the claim, or whether the term "represented by" is intended to mean that the recited hybridization conditions are merely representative or exemplary and that the claim encompasses modification(s) and variation(s) in the recited hybridization conditions.

Also, it is noted that the recited conditions appear to be only wash conditions and do not recite hybridization conditions. Even assuming *arguendo* one considers the conditions of part (a) to be hybridization conditions, it is noted that the claim fails to include a length of time for the hybridization and consequently, the scope of recited nucleic acids and thus polypeptides is unclear. The dependence of time on a nucleic acid's ability to hybridize to a target nucleic acid is evidenced by "Current Protocols in Molecular Biology" (Unit 2.10), regarding *Length of prehybridization and hybridization incubations,* which teaches, "[t]he protocols recommend prehybridization for 3 hr with nitrocellulose and 15 min for nylon membranes. Inadequate prehybridization can lead to high backgrounds, so these times should not be reduced. They can, however, be

extended without problem. Hybridizations are usually carried out overnight. This is a rather sloppy aspect of the procedure, because time can have an important influence on the result, especially if, as described above, an excess amount of a single-stranded probe is being used. The difficulties in assigning values to the parameters needed to calculate optimum hybridization time has led to the standard "overnight" incubation, which in fact is suitable for most purposes. The exception is when hybridization is being taken to its limits, for instance in detection of single-copy sequences in human DNA, when longer hybridization times (up to 24 hr) may improve sensitivity if a single-stranded probe is being used. Note that this does not apply to double-stranded probes, as gradual reannealing results in only minimal amounts of a double-stranded probe being free to hybridize after ~8 hr of incubation" (underline added for emphasis). Thus, one of skill in the art would recognize the dependence of time as being a critical parameter in determining the scope of nucleic acids that bind under the recited hybridization conditions. It is suggested that applicants clarify the meaning of the claim.

[b] Claim 18, part (b) is indefinite in the recitation of "a polynucleotide that differs from the nucleotide sequence of SEQ ID NO:1 due to the degeneracy of the genetic code, and which encodes the GUS protein." The "polynucleotide that differs from the nucleotide sequence of SEQ ID NO:1 due to the degeneracy of the genetic code" has been interpreted as meaning a degenerate variant of SEQ ID NO:1 and a skilled artisan would recognize that a degenerate variant of SEQ ID NO:1 would encode the same polypeptide as SEQ ID NO:1, *i.e.,* SEQ ID NO:2. See specification at p. 10, lines 22-24. However, it is noted that "the GUS protein" as recited in part (b) has been interpreted as

referring to the GUS protein of part (a), which encompasses variants of SEQ ID NO:2. Thus, it is unclear as to whether part (b) of claim 18 is intended as being limited to a degenerate variant of SEQ ID NO:1 that encodes SEQ ID NO:2 or whether the claim is intended as meaning a degenerate variants of SEQ ID NO:1 that encode the GUS protein that is encoded by part (a). If the latter interpretation is intended, it is unclear as to how a degenerate variant of SEQ ID NO:1, which necessarily encodes only SEQ ID NO:2, can encode GUS proteins other than SEQ ID NO:2 as encompassed by part (a). It is suggested that applicant clarify the meaning of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[11] Claims 18, 21-22, and 24-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 18 is drawn to a genus of polypeptides that are encoded by a nucleic acid that hybridizes under the recited conditions or a degenerate variant thereof. Claims 21

(claim 25 dependent therefrom), 22, and 24 are drawn to a genus of polypeptides that are encoded by a polynucleotide that has at least 80% or 90% homology to SEQ ID NO:1 and degenerate variants of a polynucleotide that has at least 80% homology to SEQ ID NO:1.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the claimed genus of GUS polypeptides, *i.e.*, SEQ ID NO:2. The specification fails to describe any additional representative species of the claimed genus of GUS polypeptides. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus," it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." In the instant case, the claimed genus of

polypeptides encompasses species that are widely variant in their structures. As such, the disclosure of the single representative species as noted above is insufficient to be representative of the attributes and features of all species of polypeptides encompassed by the claims.

Given the lack of description of a representative number of polypeptides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[12] Claims 18, 21-22, and 24-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:2, does not reasonably provide enablement for all variants of SEQ ID NO:2 as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation is required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples;

and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). MPEP 2164.04 states, "[w]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: Claim 18 is so broad as to encompass all polypeptides that are encoded by a nucleic acid that hybridizes under the recited conditions or a degenerate variant thereof. In order to determine the scope of polypeptides encompassed by claim 18, the examiner has used the well-known calculation of Meinkoth et al. (see, *e.g.,* US Patent 6,057,491, particularly column 7, lines 32-41) to provide a rough estimation of the identity between SEQ ID NO:1 and the hybridizing nucleotide sequence. According to the formula of Meinkoth et al., Tm=81.5C+16.6(log M)+0.41(%GC)-0.61(%form)-(500/L), wherein definitions of the variables used in the disclosed formula can be found in the '491 patent. According to *Molecular Biology Protocols,* (omrf.ouhsc.edu/~frank/DNAHYBRD.html, 1997; last seen on 7/13/2006), a 20X SSPE solution has the cationic molarity as follows: 3M NaCl and 0.2M NaH_2PO_4. The approximated Tm for a nucleotide sequence that hybridizes under the recited

conditions with a SEQ ID NO:1, assuming molarity of monovalent cations is 0.16 M for 1X SSPE, 33.4% GC content, and a length of 2150 bp, is 51 °C. In accordance with the teachings of Meinkoth et al. in the '491 patent, assuming that for each 1 degree Celsius the Tm is reduced from that calculated for a 100% identity hybrid, the amount of mismatch permitted is increased by about 1%. Thus, at 42 °C, the allowed mismatch is about 51-42% or about 9%. Put another way, the claims encompass nucleotide sequences that are at least about 91% identical to SEQ ID NO:1. Claims 21 (claim 25 dependent therefrom), 22, and 24 are so broad as to encompass all polypeptides that are encoded by a polynucleotide that has at least 80% or 90% homology to SEQ ID NO:1 and degenerate variants of a polynucleotide that has at least 80% homology to SEQ ID NO:1. The enablement provided by the specification is not commensurate in scope with the claim with regard to the number of polypeptides encompassed by the claim. In this case, the specification is enabling only for SEQ ID NO:2.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The amino acid sequence of a polypeptide determines the its structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.*, expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired

activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.,* multiple substitutions. At the time of the invention, methods for isolating or generating variants and mutants of a given polypeptide were known in the art. However, neither the specification nor the state of the art at the time of the invention provided the necessary guidance for altering the polypeptide of SEQ ID NO:2 with an expectation of obtaining a polypeptide having the desired activity/utility. At the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity/utility. For example, the reference of Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York) teaches "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). The teachings of Branden et al. are exemplified by the reference of Witkowski et al. (*Biochemistry* 38:11643-11650), which teaches that only a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see *e.g.*, Table 1, page 11647).

The amount of direction provided by the inventor and The existence of working examples: The specification discloses only a single working example of the claimed polypeptide, *i.e.,* SEQ ID NO:2. The specification fails to disclose any specific guidance for altering the polypeptide of SEQ ID NO:2 with an expectation that the resulting variants of SEQ ID NO:2 as encompassed by the claims will maintain the desired activity/utility.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of isolating and/or generating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen – by a trial and error process – for all polypeptides having a substantial number of modifications as encompassed by the claims for those that maintain GUS activity.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required, undue experimentation is necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is

unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Citation of Relevant Art

[13] The art made of record and not relied upon is considered pertinent to applicant's disclosure. 1) Russell et al. *Appl Environ Microbiol* 67:1253-1261, 2001 and 2) Russell "Development of Molecular Tools for the Study of Intestinal and Probiotic Lactobacilli" Dissertation, Bell and Howell Information and Learning Company, Ann Arbor, Michigan, 2002. In view of their publication dates, the cited references are not available as prior art under 35 U.S.C. 102.

Conclusion

[14] Status of the claims:

- Claims 18-19 and 21-25 are pending.
- Claims 18, 21-22, and 24-25 are rejected.
- Claims 19 and 23 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1656